Remarks

Amendments to the Claims

Claims 1-3 and 25 are amended to recite "human" NPFF1. The specification supports this amendment, for example, at page 1, lines 7-9: "[T]he present invention relates to nucleic acid sequences and amino acid sequences of a human NPFF1 . . . ."

Claims 1-3 are amended to incorporate the subject matter of canceled claim 5, *i.e.*, to recite that the contacting step occurs *in vitro*.

Claims 1-3 are amended to recite an identifying step. The specification supports this amendment on page 39, lines 19-24.

The amendment of claims 1-3 to recite agents "that may be useful . . . ." is inherent in the nature of a screening assay.

Claims 2 and 3 are amended to recite that the activity of the polypeptide results in an alteration of intracellular calcium concentration or alteration of inositol phosphate concentration. The specification supports this amendment on page 41, lines 20-24.

New claims 27-30 are supported by claims 4 and 6 as originally filed.

The amendments add no new matter.

Objection to Claims 1-3

Claims 1-3 are objected to because the word "and" was not placed between the method steps. Claims 1-3 are amended to insert the word "and" between the last two recited method steps. Claim 3 is objected to because the phrase "at the presence of a compound" is awkward. Amended claim 3 recites "in the presence of a compound."

Please withdraw the objection.

Rejection of Claims 1-11 and 25 Under 35 U.S.C. § 112 ¶ 1 (written description)

Claims 1-11 and 25 stand rejected under 35 U.S.C. § 112 ¶ 1 as failing to comply with the written description requirement. Claim 5 is canceled. Applicants respectfully traverse the rejection of claims 1-4, 6-11, and 25.

The Office Action contends that the specification only describes the NPFF1 polypeptide of SEQ ID NO:2 (*i.e.*, the claims should recite this sequence identifier). To advance prosecution, independent claims 1, 2, 3, and 25 have been amended to recite human NPFF1 polypeptides. Human NPFF1 was well known in the art before the priority date of this application. See page 4, lines 15-20 of the specification. The Court of Appeals for the Federal Circuit has held that an adequate written description of a gene which is well known in the art does not require a structural recitation either in the specification or in the claims. *See Capon v. Eshhar*, 418 F.3d 1349, 1360-61, 76 U.S.P.Q.2d 1078, 1087 (Fed. Cir. 2005) ("the Board erred in ruling that § 112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of claimed DNA, when that sequence is already known in the field."). Applying the same logic, a sequence identifier for a well-known protein such as NPFF1 should also not be required.

Whether the specification meets the written description requirement for the subject matter of claims 1-4, 6-11, and 25 is a question of fact. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991). Thus, the M.P.E.P. requires a written description rejection to set forth express findings of fact. The express findings of fact must set forth two elements:

> In rejecting a claim, **the examiner must set forth express findings of fact** which support the lack of written description conclusion. These findings should:
>
> (A) Identify the claim limitation at issue; and

> (B) Establish a *prima facie* case **by providing reasons why** a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed.

M.P.E.P. § 2163.04 ("Burden on the Examiner with Regard to the Written Description Requirement), internal reference omitted, emphasis added.

The rejection does not set forth express findings of fact to support element (B), a *prima facie* case. With respect to "human NPFF1 polypeptides," the Office Action sets forth no evidence that the genus is so varied that the specification does not describe it.

According to *Enzo Biochem, Inc. v. Gen-Probe Incorporated*, 296 F.3d 1316, 1327, 63 U.S.P.Q.2d 1609, 1615 (Fed. Cir. July 15, 2002), "the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed." One of skill in the art would readily recognize the genus of human NPFF1 polypeptides because these polypeptides were known in the art.

Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 1-11 and 25 Under 35 U.S.C. § 112 ¶ 1 (enablement)

Claims 1-11 and 25 stand rejected under 35 U.S.C. § 112 ¶ 1 as not being enabled for their full scope. Claim 5 is canceled. Applicants respectfully traverse the rejection of claims 1-4, 6-11, and 25.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art

without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). The present specification meets this standard.

To advance prosecution, several amendments have been made to independent claims 1, 2, and 3 to address points raised in the Office Action. Independent claims 1-3 have been limited to *in vitro* methods, the use of human NPFF1 polypeptides, and to screening for agents that may be useful in the treatment of the recited diseases. Independent claims 2 and 3 have been limited to recite alteration of intracellular calcium concentration as the NPFF1 activity. These amendments address the Office Action's assertions with respect to enablement of *in vivo* methods (Office Action at pages 11-12), the genus of NPFF1 polypeptides (Office Action at pages 8-10), predictability (Office Action at pages 6-7), and the modulation of other activities of NPFF1 (Office Action at page 11). The remaining assertions are addressed below.

With respect to independent claim 1, the Office Action asserts that "[t]he fact that a test compound to bind [sic; binds] to an NPFF1 polypeptide does not allow the skilled artisan [to] predict whether or not said binding partner can also alter an activity of the NPFF1 polypeptide." Office Action at page 11, lines 1-3. The Office Action further asserts that "[a] test compound can bind to a receptor without alter its activity." Office Action at page 11, lines 3-4. Claim 1 is simply a screening method for compounds which bind to a human NPFF1 polypeptide (and which therefore may be useful in the treatment of cardiovascular diseases). Claim 1 does not require identification of a test compound which binds to a human NPFF1 polypeptide as also able to alter NPFF1 activity.

The Office Action also asserts that "[n]either the specification nor the prior art teach [or] provide any reasonable correlation between NPFF1 activity and a cardiovascular disease." Office Action at page 6, lines 17-18. One of skill in the art, however, would perceive an

association of the NPFF1 polypeptide with cardiovascular disease based on the teachings of the present specification. First, it was known before this application's May 14, 2003 priority date that modulation of intracellular Ca^{2+} controls cardiac myocyte contraction. For example, Bers[1] teaches that mobilization of intracellular calcium is involved in controlling cardiac myocyte contraction: "Intracellular Ca^{2+} is the central regulator of cardiac contractility." Moreover, "it is becoming increasingly apparent that alterations in myocyte Ca^{2+} regulation may be critically important in both the mechanical dysfunction and arrhythmogenesis associated with congestive heart failure." See page 275, first paragraph. Therefore, a skilled artisan would have understood the correlation between modulating intracellular Ca^{2+} and controlling critical aspects of cardiovascular function, such as cardiac contraction.

Second, it was also known before this application's priority date that NPFF1 modulates intracellular Ca^{2+}. For example, Bonini (cited in the rejection under 35 U.S.C. § 102 (b), addressed below) teaches that the human NPFF1 receptor activates intracellular calcium mobilization in COS-7 cells expressing the recombinant receptor. See Figure 5 of Bonini.

Bonini does not report high NPFF1 expression in cardiovascular tissues.[2] The skilled artisan would obtain this information from the present specification. The specification teaches that NPFF1 is highly expressed in various cardiac tissues. Table 1 of the specification discloses high expression levels of NPFF1 in the aorta, the left ventricle, the right and left atria, and the

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[1] Bers, "Calcium Fluxes Involved in Control of Cardiac Myocyte Contraction." Circ Res. 2000:87, 275-281, provided with the accompanying IDS.

[2] Tables III and IV of Bonini display mRNA localization of NPFF1 within the entire heart. The skilled reader knows that an organ such as the heart comprises various subcompartments (*e.g.*, atrium or ventricle) in which expression of a gene could be different. The mRNA extracts of heart used to obtain the expression data disclosed in Bonini therefore represent the mean expression from all subcompartments. The high expression of NPFF1 in the aorta, the left ventricle, the right and left atria, and the pericardium, reported by the specification, was not discovered in the Bonini study because Bonini assayed all subcompartments of the heart simultaneously, rather than individual subcompartments independently.

pericardium. Thus, the specification teaches that the NPFF1 mRNA that encodes the NPFF1 polypeptide, which is known to have the ability to modulate intracellular Ca^{2+}, is highly expressed in various relevant cardiovascular tissues. Thus, no undue experimentation would be needed for the skilled artisan to associate the NPFF1 receptor with cardiovascular diseases.

Finally, the Office Action asserts that "[t]here are no examples that connect NPFF1 activity with any cardiovascular disease." Office Action at page 7, lines 21-22. It is well settled, however, that working examples are not required to enable an invention. *In re Long*, 368 F.2d 892, 895, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). The lack of a working example, therefore, should not be given undue weight because the inventors have provided adequate direction for carrying out the claimed methods.

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided in the specification. *In re Wright*, 999 F.2d 1557, 1562, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The Office Action does not provide a reasonable basis to question the enablement of claims 1-4, 6-11, and 25. Please withdraw the rejection.

Rejection of Claim 5 Under 35 U.S.C. §112 ¶ 2

Claim 5 stands rejected as indefinite under 35 U.S.C. § 112 ¶ 2. Claim 5 was canceled as redundant in light of the recitation "*in vitro*" in claim 1, which moots the rejection.

Rejection of Claims 1-11 Under 35 U.S.C. § 102(b)

The Office Action rejects claims 1-11 under 35 U.S.C. § 102(b) as anticipated by Bonini *et al.* (*J. Biol. Chem. 275*, 39324-31, 2000). Claim 5 is canceled. Applicants respectfully traverse the rejection of claims 1-4 and 6-11.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is contained in the claimed invention. *Richardson v. Suzuki Motor Co.,* 868 F.2d 1226, 1236 (Fed. Cir. 1989). Bonini does not meet this standard.

The Office Action asserts that ". . . Bonini et al teach a method of contacting a test compound ([I^{125}]1DMeNPFF) with a NPFF1 polypeptide and detecting binding of said test compound to said NPFF1 polypeptide." Office Action at page 16, lines 14-16. The Office Action further asserts that Bonini's Figure 5A "shows a comparison of the activity of NPFF1 at various concentrations of the test compound NPFF." Office Action at page 16, lines 25-26.

The amended claims recite an identifying step in which a test compound is identified as an agent that may be useful in the treatment of a cardiovascular disease if binding of the test compound to the human NPFF1 polypeptide is detected (claim 1) or if NPFF1 activity is altered in the presence of the test compound (claims 2 and 3). Bonini does not teach any association of human NPFF1 with cardiovascular disease. Thus, Bonini does not teach every element of independent claims 1-4 and 6-11.

Applicants respectfully request withdrawal of the rejection.

Respectfully submitted,

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